Express Mail Label No. EV 318 174 345 US

Date of Mailing September 29, 2003

PATENT
Case No. P1584 US
(2650/102)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
APPLICATION FOR UNITED STATES LETTERS PATENT

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TITLE: STENT WITH IMPROVED DRUG LOADING CAPACITY

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STENT WITH IMPROVED DRUG LOADING CAPACITY

TECHNICAL FIELD

This invention relates generally to biomedical devices that are used for treating vascular conditions. More specifically, the invention relates to a stent assembly that includes delivery openings to deliver a therapeutic agent.

BACKGROUND OF THE INVENTION

Stents are generally cylindrical shaped devices that are radially expandable to hold open a segment of a blood vessel or other anatomical lumen after implantation into the body lumen. Stents have been developed with coatings to deliver drugs or other therapeutic agents.

Various types of stents are in use, including balloon expandable and self-expanding stents. Balloon expandable stents generally are conveyed to the area to be treated on balloon catheters or other expandable devices. For insertion, the stent is positioned in a compressed configuration along the delivery device, for example crimped onto a balloon that is folded or otherwise wrapped about a guide catheter that is part of the delivery device. After the stent is positioned across the lesion, it is expanded by the delivery device, causing the stent diameter to expand. For a self-expanding stent, commonly a sheath is retracted, allowing expansion of the stent.

Stents are used in conjunction with balloon catheters in a variety of medical therapeutic applications including intravascular angioplasty. For example, a balloon catheter device is inflated during PTCA (percutaneous transluminal coronary angioplasty) to dilate a stenotic blood vessel. The stenosis may be the result of a lesion such as a plaque or thrombus. After inflation, the pressurized balloon exerts a compressive force on the lesion thereby increasing the inner diameter of the affected vessel. The increased

interior vessel diameter facilitates improved blood flow. Soon after the procedure, however, a significant proportion of treated vessels re-narrow or collapse.

To prevent acute vessel narrowing or collapse, short flexible cylinders, or stents, constructed of metal or various polymers are implanted within the vessel to maintain lumen size. The stents acts as a scaffold to support the lumen in an open position. Various configurations of stents include a cylindrical tube defined by a mesh, interconnected stents or like segments. Some exemplary stents are disclosed in U.S. Patent No. 5,292,331 to Boneau, U.S. Patent No. 6,090,127 to Globerman, U.S. Patent No. 5,133,732 to Wiktor, U.S. Patent No. 4,739,762 to Palmaz and U.S. Patent No. 5,421,955 to Lau. Balloon-expandable stents are mounted on a collapsed balloon at a diameter smaller than when the stents are deployed. Stents can also be self-expanding, growing to a final diameter when deployed without mechanical assistance from a balloon or like device.

Stent insertion may cause undesirable reactions such as inflammation, infection, thrombosis, and proliferation of cell growth that occludes the passageway. Stents have been used with coatings to deliver drugs or other therapeutic agents at the site of the stent that may assist in preventing these conditions. In some methods of producing a stent designed to deliver a drug, the drug coating is applied to a stent framework. This may result in the drug being delivered to only those portions of the vessel in direct contact with the stent. The coating can be applied as a liquid containing the drug or other therapeutic agent dispersed in a polymer/solvent matrix. The liquid coating then dries to a solid coating upon the stent. The liquid coating can be applied by dipping or spraying the stent while spinning or shaking the stent to achieve a uniform coating. Combinations of the various application techniques can also be used.

To increase the amount of therapeutic agent that may be deposited on the surface of the stent, the surface of the stent framework can be modified. Modifications may take the form of channels, holes or grooves on the stent surface as well as holes extending through the stent framework. However, placement of these modifications in a consistent manner is difficult leading to inconsistent amounts of drug deposition and elution.

It would be desirable, therefore, to provide a stent having a modified surface for improved drug delivery that would overcome these and other disadvantages.

SUMMARY OF THE INVENTION

One aspect of the present invention provides a method of forming a drug eluting stent, the method comprising coupling a stent framework to a mandrel, inserting the mandrel with stent framework into an open die, the die including a forming surface including a plurality of raised indention forming portions; closing the die against the stent framework; pressing the raised indention portions into the stent framework to form indentions in the stent framework; and inserting at least one drug polymer into the indentions formed in the stent framework.

Another aspect of the invention provides an apparatus for forming a drug eluting stent. The apparatus includes a mandrel, a die set including at least two portions, the at least two portions defining a channel formed through the die set for receiving the mandrel and a plurality of indentation forming portions coupled to a portion of the surface of the channel.

The foregoing and other features and advantages of the invention will become further apparent from the following detailed description of the presently preferred embodiments, read in conjunction with the accompanying drawings. The detailed description and drawings are merely illustrative of the invention, rather than limiting the scope of the invention being defined by the appended claims and equivalents thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows a stent delivery system made in accordance with the present invention;

FIG. 2 shows a coated stent made in accordance with the present invention;

FIG. 3 shows a stent made in accordance with the present invention positioned on one embodiment of a swaging apparatus;

FIG. 4 shows a cross section of a stent before swaging;

FIG. 5 shows a cross section of a stent after swaging;

FIG. 6 shows a stent made in accordance with the present invention positioned on another embodiment of a swaging apparatus;

FIG. 7 shows a top view of a bottom portion of a swaging apparatus used in accordance with the present invention;

FIG. 8 shows a top view of a bottom portion of a swaging apparatus having a dimple forming surface used in accordance with the present invention;

FIG. 9 shows a cross section of the bottom portion illustrated in **FIG. 8**;

FIG. 10 shows a detailed section of a dimpled stent segment made in accordance with the present invention;

FIG. 11 shows yet another alternate embodiment of a top view of a bottom portion of a swaging apparatus having a polished portion and a dimple forming portion made in accordance with the present invention;

FIG. 12 is a flow chart illustrating a method of manufacturing a stent in accordance with the present invention; and

FIG. 13 is a flow chart illustrating a method of using the stent manufactured in accordance with the present invention.

DETAILED DESCRIPTION OF THE PRESENTLY PREFERRED EMBODIMENT

FIG. 1 shows a stent delivery system made in accordance with the present invention. The stent delivery system **100** includes a catheter **105**, a balloon **110** operably attached to the catheter **105**, and a stent **120** disposed on the balloon **110**. The balloon **110**, shown in a collapsed state, may be any variety of balloons capable of expanding the stent **120**. The balloon **110** may be manufactured from any sufficiently elastic material such as polyethylene, polyethylene terephthalate (PET), nylon, Pebax ® polyether-block co-polyamide polymers, or the like. In one embodiment, the balloon **110** may include retention means **111**, such as mechanical or adhesive structures, for retaining the stent **120** until it is deployed. The catheter **105** may be any variety of balloon catheters, such as a PTCA (percutaneous transluminal coronary angioplasty) balloon catheter, capable of supporting a balloon during angioplasty.

The stent **120** may be any variety of implantable prosthetic devices capable of carrying a coating known in the art. In one embodiment, the stent **120** may have a plurality of identical cylindrical stent segments placed end to end. Four stent segments **121**, **122**, **123**, and **124** are shown, and it will be recognized by those skilled in the art that an alternate number of stent segments may be used.

The stent **120** includes at least one cap coating **125**, which can be applied to the stent **120** by dipping or spraying the stent **120** with a coating liquid, or applying the coating liquid with a combination of methods. The cap coating **125** can be applied as a liquid polymer/solvent matrix. A therapeutic agent can be incorporated in the cap coating **125**, or can be omitted and the cap coating **125** included for its mechanical properties alone. A coating section **130** between the cap coating **125** and the stent **120** is the primary carrier for a therapeutic agent. The cap coating **125** can be applied as a liquid containing the drug or other therapeutic agent dispersed in a polymer/solvent matrix.

The cap coating **125** can be used for a number of purposes, including, but not limited to, a diffusion barrier to control the elution rate of the therapeutic agent from the coating section **130**, a protective barrier to prevent damage to the coating section **130**, a drug carrier for the same drug as the coating section **130** or a different drug, a lubricating layer to reduce friction between the stent and the balloon of the stent delivery system, or combinations thereof. In one embodiment, the cap coating **125** can be of a single material and uniform thickness to form a concentric cap coating.

Coating section **130** may comprise one or more therapeutic agents dispersed within or encased by a polymeric coating, which are eluted from stent **120** with controlled time delivery after deployment of stent **120** within a body. A therapeutic agent is capable of producing a beneficial effect against one or more conditions including inflammation, coronary restenosis, cardiovascular restenosis, angiographic restenosis, arteriosclerosis, hyperplasia, and other diseases and conditions. For example, the therapeutic agent can be selected to inhibit or prevent vascular restenosis, a condition corresponding to a narrowing or constriction of the diameter of the bodily lumen where the stent is placed. Coating section **130** may comprise, for example, an antirestenotic drug, an antisense agent, an antineoplastic agent, an antiproliferative agent, an antithrombogenic agent, an anticoagulant, an antiplatelet agent, an antibiotic, an anti-inflammatory agent, a steroid, a gene therapy agent, an organic drug, a pharmaceutical compound, a recombinant DNA product, a recombinant RNA product, a collagen, a collagenic derivative, a protein, a protein analog, a saccharide, a saccharide derivative, a bioactive agent, a pharmaceutical drug, a therapeutic substance, or combinations thereof. The elution rates of the therapeutic agents into the body and the tissue bed surrounding the stent framework are based on the constituency and thickness of coating section **130**, the nature and concentration of the therapeutic agents, the thickness and composition of cap coating **125**, and other factors.

The cap coating **125** and coating section **130** can be a polymer including, but not limited to, urethane, polyester, epoxy, polycaprolactone (PCL), polymethylmethacrylate (PMMA), PEVA, PBMA, PHEMA, PEVAc, PVAc, Poly N-Vinyl pyrrolidone, Poly (ethylene-vinyl alcohol), combinations of the above, and the like. Suitable solvents that can be used to form the liquid coating include, but are not limited to, acetone, ethyl acetate, tetrahydrofuran (THF), chloroform, N-methylpyrrolidone (NMP), combinations of the above, and the like. Suitable therapeutic agents include, but are not limited to, antiangiogenesis agents, antiendothelin agents, antimitogenic factors, antioxidants, antiplatelet agents, antiproliferative agents, antisense oligonucleotides, antithrombogenic agents, calcium channel blockers, clot dissolving enzymes, growth factors, growth factor inhibitors, nitrates, nitric oxide releasing agents, vasodilators, virus-mediated gene transfer agents, agents having a desirable therapeutic application, combinations of the above, and the like. Specific example of therapeutic agents include abciximab, angiopeptin, colchicine, eptifibatide, heparin, hirudin, lovastatin, methotrexate, streptokinase, taxol, ticlopidine, tissue plasminogen activator, trapidil, urokinase, and growth factors VEGF, TGF-beta, IGF, PDGF, and FGF.

The cap coating **125** and coating section **130** are merely exemplary, and it should be recognized that other coating configurations, such as multiple coating layers, are possible. Although the cap coating **125** and the coating section **130** are shown schematically on the outer circumference of the stent **120**, the cap coating **125** and the coating section **130** can coat the whole stent **120**, both inside and outside, and around the cross section of individual stent wires. In another embodiment, the coating section **130** can be present on a portion of the stent **120** without a cap coating **125** on that same portion.

The different coatings can be made of the same material or different materials, and can contain the same therapeutic agents or different therapeutic agents. The coatings can be applied as a liquid polymer/solvent matrix. The liquid coating can be applied to the stent **120** by pad printing, inkjet printing, rolling, painting, spraying, micro-spraying, dipping, wiping, electrostatic deposition, vapor deposition, epitaxial growth, combinations thereof, and other methods as will be appreciated by those skilled in the art.

FIG. 2 is a side view of an illustrative embodiment of a stent used for forming a stent embodying the principles of the present invention. The stent **150** comprises a number of segments **160** each of which is made of an endless metal loop that has been bent into a plurality of straight sections or struts **155** that are integrally joined by discrete axial turns, or crowns **165**. Axially adjacent segments **160** may be joined to one another at one or more of their crowns **165**. These connections may be made by welding, soldering, adhesive bonding, mechanical fastening, or in any other suitable manner. The pattern of the segments **160** can be W-shaped or can be a more complex shape with the elements of one segment continuing into the adjacent segment. Each segment **160** may have more undulations than are shown in **FIG. 2**, but the simplified depictions shown herein will be sufficient to illustrate the present invention. The stent **150** can be installed in the stent delivery system of **FIG. 1** for implantation in a body lumen.

Referring to **FIG. 2**, the stent **150** is conventional to stents generally and can be made of a wide variety of medical implantable materials, such as stainless steel (particularly 316-L stainless steel or 316LS), cobalt base alloys, nitinol, tantalum, ceramic, nickel, titanium, aluminum, polymeric materials, tantalum, MP35N, titanium ASTM F63-83 Grade 1, niobium, high carat gold K 19-22, and combinations thereof. The stent **150** can be formed through various methods as well. The stent **150** can be welded, laser cut, molded, or consist of filaments or fibers which are wound or braided together in order to form a

continuous structure. Although segments **160** may or may not be made of what would be regarded in some other arts as wire, the material of segments **160** is generally wire-like, and so the term "wire" is sometimes used herein to refer to such stent material. Depending on the material and design, the stent can be self-expanding, or be expanded by a balloon or some other device. The cap coating and coating section can be on the surface of the segments **160**.

Referring now to **FIGS. 3** to **5**, the manufacture of the drug eluting stent according to the present invention begins with a conventional stent such as the stent illustrated in **FIG. 2**. After the stent is formed, the stent undergoes a swaging (profiling) process. This process is described in commonly owned co-pending U.S. Patent Application No. 10/029,553 titled “Profiled Stent and Method of Manufacture” by Matthew J. Birdsall, the entirety of which is incorporated by reference. During this process, the profile of the stent struts are altered as best illustrated in **FIGS. 4** and **5**. **FIG. 4** shows a cross section through stent struts **400** of a closed stent positioned on mandrel **420** before the profiling process. The cross section of the stent struts **400** before the process is of a generally circular nature. **FIG. 5** shows the same closed stent section after undergoing the profiling process. After the procedure, the cross section of the stent strut **400** is of a generally ellipto-rectangular nature.

FIG. 3 illustrates the rotary swaging device **200** for profiling a stent **222**. The swaging device **200** includes a die set **210** and a swaging mandrel **220**. The die set **210** illustrated includes two parts, a top portion **212** and a bottom portion **214**. The stent **222** is disposed upon the swaging mandrel **220** before insertion into the swaging die set **210**. The swaging mandrel **220** may include a collar portion (not shown) to prevent the stent **222** from sliding off the mandrel **220** during the profiling process.

The top portion **212** and a bottom portion **214** each have a semicircular channel **216** that is polished to a mirror finish. This polished surface aids in removing any defects on the stent surface and smoothing the stent surface. In the closed position, the semicircular channel **216** has a diameter that is less than that of the stent **222** positioned on the mandrel **220**. In one embodiment, the diameter of the semicircular channel **216** in the fully closed position is approximately 0.0002 – 0.0015 inch less than that of the stent positioned on the mandrel.

FIG. 7 illustrates the inside face of bottom portion **214**. The semicircular channel **216** is slightly tapered toward the inside of the die in a funnel like manner to facilitate the entry of the stent into the die and to accommodate the increased diameter of the stent before profiling as compared to the stent diameter after profiling. **FIG. 7** also illustrates the connection means for operably connecting top portion **212** to a bottom portion **214**. Top portion **212** and a bottom portion **214** are connected via a pair of springs (not shown) that are each disposed in spring seats **218**. The springs aid in the translation of the top portion **212** and a bottom portion **214** relative to each other during the profiling process.

Returning now to **FIG. 3**, during the swaging process, the stent is swaged by passing the stent **222** and swage mandrel **220** through the rotating die set **210** while the die set is repeatedly opened and closed. The closed die forces the stent to conform to the annular space defined between the mandrel **220** and the closed die set **210**. As stated above, in the fully closed state, the diameter of the swage die set channel is less than the outer diameter of the stent positioned on the mandrel. The effect is a reduction of the stent strut thickness. Furthermore, the profile of the stent is changed as described above in relation to FIGS. 4 and 5.

In a preferred embodiment, the entire stent is profiled. The stent however could be preferentially profiled by profiling only the struts **155** or only the crowns **165** where most of the stress occurs in the instance of a multi-section stent, or by selectively profiling one or more stent sections.

Other methods for swaging a stent are available. In one preferred embodiment of the present invention, a stent is profiled by swaging the stent by either using a swaging machine or by using a collet. In another embodiment, the stent is profiled using a roller method. In yet another embodiment, the stent is profiled using a sizing tube and forming tool. A non-rotary swage machine is also suitable.

FIG. 6 is a block diagram illustrating another embodiment of a swaging assembly **600**. **FIG. 6** shows the profiling of stent **622** using a collet **610**. Similar to the rotary swage machine **200**, a conventional stent is placed over mandrel **620** which is in turn placed into the collet **610**. Collet **610** comprises four wedge shaped portions **612, 614, 616, 618** that define a polished channel similar to that of swaging die set **210**. Collet **610** is closed, forcing the stent to conform to the annular space defined between the mandrel **620** and the closed collect **610**.

Referring now to **FIGS. 8-10**, an apparatus for improving the drug loading capacity of a profiled stent is illustrated in accordance with the present invention. In order to improve the drug loading capacity of a stent, the present invention modifies the surface of a stent. The modification is in the form of providing a plurality of dimples, or indentations, to the surface of the stent. This is accomplished by altering the channel surface of the top and bottom portions of a die set similar to that illustrated in **FIG. 3**.

FIG. 8 illustrates the top view of the bottom portion **314** and **FIG. 9** illustrates a cross section of the bottom portion **314** of a die set similar to the die set **210** used in the profiling process described above. However, the forming surface of the semicircular channel of the bottom portion **314** and top portion (not shown) has been modified to include a plurality of raised indention forming portions **317**. The indention forming portions **317** form dimples on the surface of the stent framework when the die set is closed upon a stent positioned on a mandrel that has been inserted into the modified die assembly. The die set can be repeatedly opened, the mandrel with the stent repositioned, and the die set

closed in order that the surface of the stent is covered with indentations due to pressing the indentation forming portions onto the surface of the stent. **FIG. 10** illustrates a portion of a stent having undergone the dimple forming process. Stent segment **760** is shown having a plurality of indentation or dimples **770**.

Those of ordinary skill in the art will recognize that the pattern of dimples may be varied. The number and size of the indention forming portions **317** may be varied to increase or decrease the amount of therapeutic agent coated on the stent. Those of ordinary skill in the art will recognize that the shape of the indention forming portions **317** may also be varied depending on the application.

The indention forming portions **317** on the forming surface of the semicircular channel may be produced by several methods. For example, the indention forming portions **317** may be welded onto the surface of the channel. Other methods include, but are not limited to, photochemical etching, lithography, bead blasting and electrodeposition.

FIG. 11 illustrates another embodiment **500** of the die set in accordance with the present invention. In the embodiment illustrated in **FIGS. 8** and **9**, the stent is profiled in one die set and moved to another die set for dimpling. In the embodiment illustrated in **FIG. 11** a single die set is used. **FIG. 11** illustrates the bottom portion of a two piece die set having a mirror finished portion **540** for profiling the stent and an indentation forming portion **560** for forming the dimples on the stent.

FIG. 12 is a flow chart depicting the process **800** of producing a coated stent in accordance with the present invention. The process 800 begins by manufacturing a conventional stent, (**Step 810**). The particular type of stent manufactured may include self-expandable stents or balloon-expandable stents, and tubular-slotted stents or wire-like stents as described above.

After the stent is manufactured, the stent is swaged in order to provide a profiled stent of a desired thickness (**Step 820**). After swaging, the profiled stent is annealed (**Step 830**) to soften and de-stress the material comprising the stent. After annealing, the stent is electro-polished (**Step 840**). The stent is then inserted into an indentation forming die set to dimple the surface of the stent (**Step 845**). The stent may be repositioned as often as necessary to provide the desired number and pattern of individual dimples.

The dimpled stent may then be coated (**Steps 850** to **900**). A first polymer and drug (or other therapeutic agent) are mixed with a first solvent to form a polymer/drug solution (**Step 850**). The polymer/drug solution is applied to the stent and inserted into the indentations on the dimpled surface in a coating layer (**Step 860**) and the coating layer cured to form a drug polymer coating (**Step 870**). A second polymer is mixed with a second solvent to form a polymer solution (**Step 880**). The polymer solution is applied to the drug polymer coating in a cap layer (**Step 890**) and the cap layer cured to form a cap coating (**Step 900**).

If the stent is self expanding, then the stent can be placed on a catheter. If the stent is a balloon inflatable stent, then the stent is crimped onto a balloon catheter for subsequent insertion into a lumen.

Those skilled in the art will appreciate that the method of manufacturing can be varied for the materials used and the results desired. For certain polymer/drug solutions and polymer solutions, the curing step can be omitted or can be a simple drying process. In another embodiment, the first polymer and first solvent can be the same combination as the second polymer and second solvent. In yet another embodiment, the polymer solution can also contain a drug or other therapeutic agent.

FIG. 13 shows a flow diagram of a method for deploying a drug-polymer coated stent in a vessel, in accordance with one embodiment of the present invention at **1000**. Coated stent deployment method **1000** includes various steps to deploy a drug-polymer coated stent in a vessel in a body.

A drug-polymer coated stent is positioned in a vessel in the body, (**Step 1010**). The vessel may be located in one of many vessels within the cardiovascular system, or in other vascular systems within the body such as the cerebrovascular system, the urinogenital system, biliary conduits, abdominal passageways, or peripheral vasculature. A catheter coupled to the drug-polymer coated stent in conjunction with a guide wire is inserted into one of the vessels of the body such as the femoral artery, and the coated stent is guided through one or more vessels into a directed location within the body. The coated stent position may be monitored, for example, using radiopaque markers or radiopaque fluid with associated x-ray imaging systems. The guide wire and catheter are manually manipulated through the vascular system to the desired location for stent deployment.

The balloon is inflated, (**Step 1020**). The balloon is filled with a liquid such as a contrast fluid that is fluidly coupled through the catheter from a source external to the body. As pressure is applied to the fluid, the balloon enlarges. As the balloon expands, a coated stent surrounding the balloon expands.

The coated stent is deployed, (**Step 1040**). The coated stent is deployed with the balloon. The coated stent is enlarged and is secured against the tissue bed of the vascular wall. The size of the deployed stent is determined in part by the maximum pressure applied to the fluid when inflating the balloon.

The balloon is deflated after the coated stent is deployed, (**Step 1050**). The pressure applied to the interior of the balloon is reduced and the coated stent separates from the balloon. Liquid in the balloon may be pumped out, collapsing the balloon even further. The balloon and catheter are then withdrawn from the vessel.

It is important to note that **FIGS. 1-13** illustrate specific applications and embodiments of the present invention, and is not intended to limit the scope of the present disclosure or claims to that which is presented therein. For example, the cap coating and coating layer can be applied in a variety of conventional ways, including painting, spraying, dipping, wiping, electrostatic deposition, vapor deposition, epitaxial growth, combinations thereof, and other methods known to those of ordinary skill in the art. The means of applying the liquid coating, such as spray nozzles or pads, can be moved in various paths relative to the stent to achieve particular patterns and thickness variations. Upon reading the specification and reviewing the drawings hereof, it will become immediately obvious to those skilled in the art that myriad other embodiments of the present invention are possible, and that such embodiments are contemplated and fall within the scope of the presently claimed invention.

While the embodiments of the invention disclosed herein are presently considered to be preferred, various changes and modifications can be made without departing from the spirit and scope of the invention. The scope of the invention is indicated in the appended claims, and all changes that come within the meaning and range of equivalents are intended to be embraced therein.

ABSTRACT OF THE DISCLOSURE

The present invention provides a method of forming a drug eluting stent, the method comprising coupling a stent framework to a mandrel, inserting the mandrel with stent framework into an open die, the die including a forming surface including a plurality of raised indention forming portions; closing the die against the stent framework; pressing the raised indention portions into the stent framework to form indentions in the stent framework; and inserting at least one drug polymer into the indentions formed in the stent framework.